VERIFICATION OF TRANSLATION

I, Harumi Endo, of 9-1, Oe-cho, Minato-Ku, Nagoya-shi, Aichi 455-8502 Japan hereby declare that I am competent in both the Japanese and English languages and that the attached English language translation is an accurate translation of Japanese 2002-260376 filed September 5, 2002.

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signature: Harumi Endo

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[List of Submitted Items]

[Name of Item] Specification 1

[Name of Item] Abstract 1

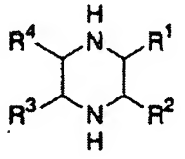
[Requirement of Proof] Necessary

[Document Name] Specification

[Title of the Invention] Process for producing a piperazine derivative

[Claims]

[Claim 1] A process for producing a piperazine derivative, in which a piperazine derivative represented by general formula (1) is oxycarbonylated to produce an oxycarbonyl-substituted piperazine derivative represented by general formula (2)



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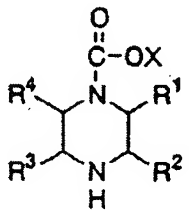
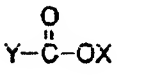


(2)

(where R^1, R^2, R^3 and R^4 denote, respectively independently, i) a hydrogen atom, ii) an alkyl group with 1 to 4 carbon atoms, iii) an alkoxy group with 1 to 4 carbon atoms, iv) a halogen group, v) a carboxyl group, vi) a carbamoyl group, or vii) an N-alkylcarbamoyl group with 1 to 4 carbon atoms in its alkyl group; X denotes i) an alkyl group with 1 to 4 carbon atoms, ii) an alkenyl group with 1 to 4 carbon atoms, iii) an alkynyl group with 1 to 4 carbon atoms, iv) an aralkyl group not substituted in the aromatic ring, or substituted by an alkyl group with 1 to 4 carbon atoms or by an alkoxy group with 1 to 4 carbon atoms or by a halogen group, or v) an aryl group not substituted in the aromatic ring, or substituted by an alkyl

group with 1 to 4 carbon atoms or by an alkoxy group with 1 to 4 carbon atoms or by a halogen group; excluding the case where all of R^1, R^2, R^3 and R^4 denote a hydrogen atom respectively), characterized in that an organic solvent with a water content of 15 wt% or less is used.

[Claim 2] A process for producing a piperazine derivative, according to claim 1, wherein a reagent represented by general formula (3) or general formula (4)



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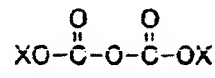


(4)

(where X denotes i) an alkyl group with 1 to 4 carbon atoms, ii) an alkenyl group with 1 to 4 carbon atoms, iii) an alkynyl group with 1 to 4 carbon atoms, iv) an aralkyl group not substituted in the aromatic ring, or substituted by an alkyl group with 1 to 4 carbon atoms or by an alkoxy group with 1 to 4 carbon atoms or by a halogen group, or v) an aryl group not substituted in the aromatic ring, or substituted by an alkyl group with 1 to 4 carbon atoms or by an alkoxy group with 1 to 4 carbon atoms or by a halogen group; Y denotes halogen atom) is used.

[Claim 3]

The process for producing a piperazine derivative, according to Claim 1 or 2, wherein R^2 in the general formulas (1) and (2) is a methyl group.

[Claim 4]

The process for producing a piperazine derivative, according to Claim 1, 2, or 3, wherein X in the general formula (2) is a t-butyl group or a benzyl group.

[Claim 5]

The process for producing a piperazine derivative, according to Claim 2, 3, or 4, wherein the reagent shown in the general formula (3) or (4) is benzyl chlorocarbonate or ditert-butyldicarbonate.

[Claim 6]

The process for producing a piperazine derivative, according to Claim 1, 2, 3, 4, or 5, wherein the organic solvent is alcohol.

[Claim 7]

The process for producing a 2-methylpiperazine derivative, according to Claim 1, 2, 3, 4, 5, or 6, wherein R^1, R^3, and R^4 in the general formulas (1) and (2) are a hydrogen atom, R^2 is a methyl group, and the compound represented with the general formulas (1) and (2) is an optically active substance.

[Detailed Description of the Invention]

[0001]

[Technical Field of the Invention]

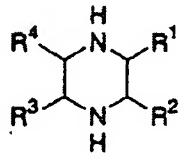
The present invention relates to a process for producing an oxycarbonyl-substituted piperazine derivative by

oxycarbonylating a piperazine derivative.

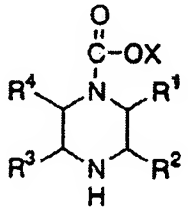
[0002]

Various methods are known as reactions for oxycarbonylating amino groups. As a reaction method for it, in which a piperazine derivative represented by general formula (1) is oxycarbonylated to produce an oxycarbonyl-substituted piperazine derivative represented by general formula (2)

[0003]



(1)



(2)

[0004]

(where R^1, R^2, R^3 and R^4 denote, respectively independently, i) a hydrogen atom, ii) an alkyl group with 1 to 4 carbon atoms, iii) an alkoxy group with 1 to 4 carbon atoms, iv) a halogen group, v) a carboxyl group, vi) a carbamoyl group, or vii) an N-alkylcarbamoyl group with 1 to 4 carbon atoms in its alkyl group; X denotes i) an alkyl group with 1 to 4 carbon atoms, ii) an alkenyl group with 1 to 4 carbon atoms, iii) an alkynyl group with 1 to 4 carbon atoms, iv) an aralkyl group not substituted in the aromatic ring, or substituted by an alkyl group with 1 to 4 carbon atoms or by an alkoxy group with 1 to 4 carbon atoms or by a halogen group, or v) an aryl group not

substituted in the aromatic ring, or substituted by an alkyl group with 1 to 4 carbon atoms or by an alkoxy group with 1 to 4 carbon atoms or a halogen group; excluding the case where all of R^1, R^2, R^3 and R^4 denote a hydrogen atom respectively), the so-called Schotten-Baumann's method for performing a two-phase system reaction in a mixed solvent of an organic solvent-water under an alkaline condition is employed. Detailed reaction conditions for the method are described in non-patent reference 1 and non-patent reference 2. For example, in the former, benzyl chlorocarbonate is used for performing benzyloxycarbonylation (Z-protection) in a sodium carbonate aqueous solution. Furthermore, in the latter, as an experimental example, the amino groups in kanamycin A sulfate were Z-protected using 1.3 eq. of Z-Cl. The reaction solvent was a mixed solvent of methanol/water = 17/83 (ratio by weight). The yield was as low as 64%.

[0005]

On the other hand, Reference Example 10 of patent reference 1 was carried out using 0.25 molar time, based on the amount of 2-methylpiperazine, of Z-Cl in dichloromethane solvent at a very low temperature of -78°C difficult to achieve industrially in general equipment. In this case, for inhibiting the side reaction by Z-Cl, 2-methylpiperazine more substrative than Z-Cl was used in a large amount for carrying out at a very low temperature. The yield based on the amount

of Z-Cl was 85%, while the yield based on the amount of the substrate was 21%. In the case where an expensive substrate like an optically active substance is used, a method of 1 or more in the molar ratio of substrate/Z-Cl is economically disadvantageous. Furthermore, in non-patent reference 3, acylation, especially Z-protection, benzoylation, tert-butoxycarbonylation (Boc-protection), etc. are performed using an N-mesyl-N-acylaniline derivative, but since it is necessary to synthesize an oxycarbonylating agent separately, the method cannot be said to be industrially efficient.

[0006]

[Patent reference 1]

JP2001-328938A

[Non-patent reference 1]

"Protective Groups in Organic Synthesis" (John Wiley & Sons Inc., 1980), p. 218

[Non-patent reference 2]

Organic Chemistry 4 - Synthetic Reactions [II]) - (Kagaku Dojin, 1990), p. 24

[Non-patent reference 3]

J. Chem. Soc., Perkin Trans. 1, 2973 (1998)

[0007]

[Problem to be Solved by the Invention]

So, in the case where a water-soluble piperazine derivative is made to react by a method described in literatures

for a liquid-liquid two-phase system, the yield of the oxycarbonyl-substituted piperazine derivative is as low as less than 50%. It was found that the byproduct in which both the two nitrogen atoms of the piperazine provided as the raw material are substituted by oxycarbonyl groups is produced more than the intended oxycarbonyl-substituted piperazine derivative. Therefore, it is demanded to create a simple method for producing an oxycarbonyl-substituted piperazine derivative at a high yield. The object of this invention is to provide a process for producing an oxycarbonyl-substituted piperazine derivative at a high yield by oxycarbonylating a piperazine derivative.

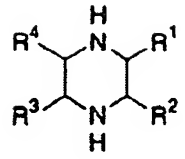
[0008]

[Means for Solving the Problem]

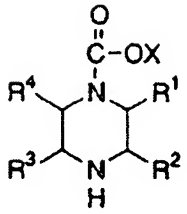
The inventors studied intensively on the process for producing an oxycarbonyl-substituted piperazine derivative by oxycarbonylating a piperazine derivative, and completed the present invention. That is, this invention is a process for producing a piperazine derivative, in which a piperazine derivative represented by general formula (1) is oxycarbonylated to produce an oxycarbonyl-substituted piperazine derivative represented by general formula (2)

[0009]

[Formula 4]



(1)



(2)

[0010]

(where R^1, R^2, R^3 and R^4 denote, respectively independently, i) a hydrogen atom, ii) an alkyl group with 1 to 4 carbon atoms, iii) an alkoxy group with 1 to 4 carbon atoms, iv) a halogen group, v) a carboxyl group, vi) a carbamoyl group, or vii) an N-alkylcarbamoyl group with 1 to 4 carbon atoms in its alkyl group; X denotes i) an alkyl group with 1 to 4 carbon atoms, ii) an alkenyl group with 1 to 4 carbon atoms, iii) an alkynyl group with 1 to 4 carbon atoms, iv) an aralkyl group not substituted in the aromatic ring, or substituted by an alkyl group with 1 to 4 carbon atoms or by an alkoxy group with 1 to 4 carbon atoms or by a halogen group, or v) an aryl group not substituted in the aromatic ring, or substituted by an alkyl group with 1 to 4 carbon atoms or by an alkoxy group with 1 to 4 carbon atoms or by a halogen group; excluding the case where all of R^1, R^2, R^3 and R^4 denote a hydrogen atom respectively), characterized in that an organic solvent with a water content of 15 wt% or less is used. The oxycarbonyl-substituted piperazine derivative in this invention can also be a racemic modification or optically active substance.

[0011]

[Embodiment of the Invention]

The present invention will be described below in detail.

[0012]

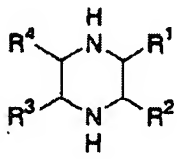
A particular method of this reaction will be exemplified.

[0013]

The piperazine derivative represented by general formula (1) and used in this invention

[0014]

[Formula 5]



(1)

[0015]

(where R^1, R^2, R^3 and R^4 denote, respectively independently, i) a hydrogen atom, ii) an alkyl group with 1 to 4 carbon atoms, iii) an alkoxy group with 1 to 4 carbon atoms, iv) a halogen group, v) a carboxyl group, vi) a carbamoyl group, or vii) an N-alkylcarbamoyl group with 1 to 4 carbon atoms in its alkyl group; excluding the case where all of R^1, R^2, R^3 and R^4 denote a hydrogen atom respectively) is a piperazine derivative substituted by one to four substituent groups. Examples of it include 2-methylpiperazine, 2-ethylpiperazine,

2,3-dimethylpiperazine, 2-methoxypiperazine, 2-isopropoxypiperazine, 2-methoxy-5-n-butoxypiperazine, 2-chloropiperazine, 2-bromopiperazine, 2,6-dichloropiperazine, 2-methyl-3-chloropiperazine, 2-piperadinecarboxylic acid, 2-ethyl-3-piperazinecarboxylic acid, 2-tert-butyl-3-piperazinecarboxylic acid, 2-piperazinecarboxamide, 2-ethyl-3-piperazinecarboxamide, 2-tert-butylcarboxamide, 3-methoxy-2-tert-butylcarboxamide, 2-n-butylcarboxamide, etc. Preferred are piperazine, 2-methylpiperazine, 2-ethylpiperazine and 2,3-dimethylpiperazine. More preferred is 2-methylpiperazine. Any of them can also be a racemic modification or optically active substance.

[0016]

Furthermore, the piperazine derivative can be in a free state or can also form a salt. Examples of it include tartaric acids such as p-, p'-ditoluoyltartaric acid (PTTA) salt, o-, o'-ditoluoyltartaric acid (OTTA) salt, dibenzoyltartaric acid (DBTA) salt, and p-, p'-dianisoyltartaric acid (DATA) salt, benzoic acids such as benzoic acid salt, 3,5-dinitrobenzoic acid salt and 1,3-benzenedicarboxylic acid salt, mineral acid salts such as phenol salts, hydrochloric acid, sulfuric acid salts, nitric acid salts and phosphoric acid salts of phenol, nitrophenol, resorcinol, catechol, etc., metal halide salts such as copper tetrachloride salt, copper tetrabromide salt and

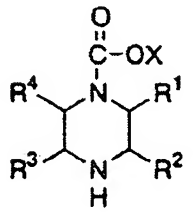
cobalt trichloride salt, etc. Preferred is a salt of tartaric acid and any of its derivatives.

[0017]

Now, the oxycarbonyl-substituted piperazine derivative obtained in this invention is represented by general formula (2):

[0018]

[Formula 6]



(2)

[0019]

(where R^1, R^2, R^3 and R^4 denote, respectively independently, i) a hydrogen atom, ii) an alkyl group with 1 to 4 carbon atoms, iii) an alkoxy group with 1 to 4 carbon atoms, iv) a halogen group, v) a carboxyl group, vi) a carbamoyl group, or vii) an N-alkylcarbamoyl group with 1 to 4 carbon atoms in its alkyl group; X denotes i) an alkyl group with 1 to 4 carbon atoms, ii) an alkenyl group with 1 to 4 carbon atoms, iii) an alkynyl group with 1 to 4 carbon atoms, iv) an aralkyl group not substituted in the aromatic ring, or substituted by an alkyl group with 1 to 4 carbon atoms or by an alkoxy group with 1 to 4 carbon atoms or by a halogen group, or v) an aryl group not

substituted in the aromatic ring, or substituted by an alkyl group with 1 to 4 carbon atoms or by an alkoxy group with 1 to 4 carbon atoms or by a halogen group; excluding the case where all of R^1, R^2, R^3 and R^4 denote a hydrogen atom respectively), and it is preferred that X denotes a tert-butyl group or benzyl group. Examples include 1-methoxycarbonylpiperazine, 1-methoxy-2-methylpiperazine, 1-methoxyl-3-methylpiperazine, 2-ethyl-1-methoxycarbonylpiperazine, 1-ethoxycarbonyl-2-methylpiperazine, 1-tert-butoxycarbonylpiperazine, 1-tert-butoxycarbonyl-2-methylpiperazine, 1-tert-butoxycarbonyl-3-methylpiperazine, 1-tert-butoxycarbonyl-2,3-dimethylpiperazine, 1-tert-butoxy-2-methoxy-3-methylpiperazine, 1-vinyloxycarbonylpiperazine, 1-vinyl-2-methylpiperazine, 1-vinyl-3-methylpiperazine, 1-allyloxycarbonylpiperazine, 1-allyl-2-methylpiperazine, 1-allyl-3-methylpiperazine, 1-methylpropinyloxycarbonylpiperazine, 1-benzyloxycarbonylpiperazine, 1-benzyloxycarbonyl-2-piperazine, 1-benzyloxycarbonyl-3-methylpiperazine, 1-benzyloxy-3,5-dimethylpiperazine, 1-benzyloxycarbonyl-3-methoxypiperazine, 1-(p-methylphenylmethyl)oxycarbonylpiperazine, 1-(p-methylphenylmethyl)oxycarbonyl-3-methylpiperazine,

1-phenoxycarbonylpiperazine,

1-phenoxycarbonyl-2-methylpiperazine,

1-phenoxycarbonyl-3-methylpiperazine,

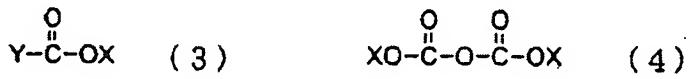
1-phenoxycarbonyl-2,5-dimethylpiperazine, etc. These compounds can be synthesized from general formula (1), and can be either racemic modifications or optically active substances.

[0020]

As the reagent used for oxycarbonylation, those described in "Protective Groups in Organic Synthesis" (John Wiley & Sons Inc., 1980) can be used. Particularly those having a structure represented by general formula (3) or general formula (4):

[0021]

[Formula 7]



(3) (4)

[0022]

(where X denotes i) an alkyl group with 1 to 4 carbon atoms, ii) an alkenyl group with 1 to 4 carbon atoms, iii) an alkynyl group with 1 to 4 carbon atoms, iv) an aralkyl group not substituted in the aromatic ring, or substituted by an alkyl group with 1 to 4 carbon atoms or by an alkoxy group with 1 to 4 carbon atoms or by a halogen group, or v) an aryl group not substituted in the aromatic ring, or substituted by an alkyl group with 1 to 4 carbon atoms or by an alkoxy group with 1 to

4 carbon atoms or by a halogen group) can be preferably used, and include chlorocarbonate esters typified by methyl chlorocarbonate, ethyl chlorocarbonate, vinyl chlorocarbonate, allyl chlorocarbonate, phenyl chlorocarbonate, benzyl chlorocarbonate, p-bromobenzyl chlorocarbonate, etc., and dicarbonate esters such as dimethyl dicarbonate, diethyl dicarbonate, di-tert-butyl dicarbonate (DiBoc), diphenoxy dicarbonate and dibenzyloxy dicarbonate. Preferred are chlorocarbonate esters such as benzyl chlorocarbonate and ethyl chlorocarbonate, and di-tert-butyl dicarbonate (DiBoc).

[0023]

The amount of it added is usually 0.9 to 1.2 moles, preferably 0.95 to 1.1 moles, more preferably 0.98 to 1.05 moles based on the amount of the piperazine derivative provided as the raw material. In the case of 1 mole or more, the reagent is more likely to be bound to the two nitrogen atoms of the piperazine derivative, and on the other hand, in the case of less than 1 mole, the piperazine derivative is likely to remain as an unreactive raw material. Therefore, it is preferred to change the amount used in response to each purpose.

[0024]

The conditions for adding the reagent are not especially limited. In general, dropwise addition is performed in a temperature range from -25 to 60°C, preferably in a range from -10 to 40°C, more preferably from -5 to 30°C. The addition time

period can be adjusted in response to the temperature and is not especially limited. However, it is usually from 2 to 12 hours.

[0025]

The organic solvent used for the reaction can be soluble or insoluble in water. However, an organic solvent of 1 wt% or more in the mutual solubility with water at 20°C is preferred.

[0026]

Furthermore, it is important that water content of the organic solvent is 15 wt% or less. If the water content is more than 15 wt%, there arises a problem, since the reaction yield of the oxycarbonyl piperazine derivative obtained by oxycarbonylating the piperazine derivative is remarkably lowered.

[0027]

Meanwhile, the water content of the organic solvent used for the reaction can be obtained using a Karl Fischer water content meter.

[0028]

The water content used in this invention does not mean the rate of only the water homogeneously dissolved in the organic solvent, but means the rate of the water forming a two-phase system due to separation from the organic solvent. For example, in a water-toluene system, water-1-butanol system or the like, water can exist separately in the lower layer while

the organic solvent can exist in the upper layer, and such a case is included. In this case, the water contents in the respective upper and lower layers can be individually measured, and the water content of the organic solvent can be calculated from the following calculation formula: (Water content of the organic solvent) = 100 x (Water content of the upper layer x Weight of the upper layer + Water content of the lower layer x Weight of the lower layer)/(Weight of the upper layer + Weight of the lower layer).

[0029]

Examples of the organic solvent include alcohols such as methanol, ethanol, 1-propanol, isopropanol, 1-butanol, 2-butanol, isobutanol, 1-pentanol, 2-pentanol and isopentanol, ethers such as diethyl ether, diisopropyl ether, di-n-propyl ether, 1,4-dioxane, 1,3-dioxane and methyl-tert-butyl ether, ketones such as acetone, methyl ethyl ketone, methyl isobutyl ketone, 2-pentanone and 3-pentanone, aromatic hydrocarbons such as benzene, toluene, ethylbenzene, o-xylene, m-xylene and p-xylene, and aliphatic hydrocarbons such as pentane, n-hexane, isohexane, cyclohexane and octane. Preferred are alcohols such as methanol, ethanol, 1-propanol, isopropanol, 1-butanol, 2-butanol, isobutanol, 1-pentanol, 2-pentabol and isopentanol, and ethers such as diethyl ether, diisopropyl ether, di-n-propyl ether, 1,4-dioxane, 1,3-dioxane and methyl-tert-butyl ether. More preferred are alcohols such as

methanol, ethanol, 1-propanol, isopropanol, 1-butanol, 2-butanol, isobutanol, 1-pentanol, 2-pentanol and isopentanol. Further more preferred are lower alcohols such as methanol, ethanol, 1-propanol, isopropanol, 1-butanol, 2-butanol and isobutanol. Any one of these solvents can be used, or plural organic solvents can also be used as a mixed solvent. Furthermore, a solvent containing water can be a homogeneous solution or can also be separated in phase. However, the state of a homogeneous solution is preferred.

[0030]

The amount of the organic solvent used is not especially limited, and is used to ensure that the concentration of the piperazine derivative before adding the reagent is from 5 to 20 wt%.

[0031]

The oxycarbonylpiperazine derivative obtained in such way often forms a salt in a reaction solution, the salt separated by concentration etc. can be collected by filtration, and it can also be collected in a free state by extracting under an alkaline condition.

[0032]

The process in the present invention uses the general formula (1) that is optically active as a raw material, and it is suitable to obtain the general formula (2) that is optically active.

[0033]

The piperazine derivative obtained as described above is a compound useful, for example, as a raw material of medicines.

[0034]

[Example]

This invention is described below in detail in reference to examples, but is not limited thereto or thereby.

[0035]

The product content and the main byproduct contents of the reaction solution and the optical purity of the product were analyzed by means of liquid chromatography respectively under different analytical conditions. The optical purity was calculated from the area ratio of R-isomer peak and S-isomer peak. In the case where S-isomer was selectively produced, calculation from the following formula was made.

[0036]

Optical purity (%ee) = {(Area value of S-isomer peak - Area value of R-isomer peak)/(Area value of S-isomer peak + Area value of R-isomer peak)} x 100(%)

Here, analysis conditions of a z-protection reaction of 2-methylpiperazine are shown below.

[0037]

<Content Analysis>

Model: Shimadzu LC-10Vp

Column: Capcellpak C18, 120 angstroms, 5 μm, 4.6 mm x 250 mm

(Shiseido)

Mobile phase: 5 mM sodium dodecyl sulfate aqueous solution (adjusted to pH 2.5 using phosphoric acid)/CH_3CN = 69/31 (0-15 min), 55/45 (25-40 min)

Flow rate: 1.0 ml/min

Temperature: 40°C

Detector: UV (210 nm)

<Optical Purity Analysis>

Model: Shimadzu LC-10Vp

Column: Mightysil RP-18 GP, 4.6 mm x 150 mm (Kanto Kagaku)

Mobile phase: 0.03 v/v% ammonia aqueous solution (adjusted to pH 4.7 using acetic acid)/CH_3CN = 65/35 (v/v)

Flow rate: 1.0 ml/min

Temperature: 40°C

Detector: UV (243 nm)

Pretreatment of sample

A sample corresponding to about 0.1 g of 1-benzyloxycarbonyl-3-methylpiperazine is placed in a 50 ml measuring flask, and acetonitrile is used for dilution up to the marked line. Then, 0.3 ml of the solution was placed in a 5 ml sample bottle, and 1.5 ml of p,p'-ditoluoyltartaric anhydride (D-PTAN) solution is added, being followed by stirring and subsequent standing in a 70°C warm bath for 1 hour. Subsequently 0.5 ml of 2% phosphoric acid water is added, being followed by standing for 10 minutes.

[0038]

Water content of the organic solvent is measured using a Karl Fischer water content meter.

[0039]

Example 1

5.0 g (= 0.0499 mol) of racemic 2-methylpiperazine was placed in a 100 ml four-neck flask, and 44 g of 1-butanol (water content 0.05 wt%) was added and dissolved. The solution was cooled to 0°C, and 8.47 g of benzyl chlorocarbonate (= 0.0489 mol, purity 98.5 wt% by HPLC quantitative analysis) was added dropwise in a liquid temperature range of 0 to 8°C. Then, stirring was carried out at 0°C for 2 hours, the solution was made uniform by adding water to this slurry, the reaction solution was partially sampled, and it was determined quantitatively by the internal standard method (internal standard: anisole). As a result, the reaction yield of 1-benzyloxycarbonyl-3-methylpiperazine was 83.9% (based on the amount of 2-methylpiperazine). When the reaction solution was further stirred at 25°C for 12 hours and analyzed, the reaction yield was 85.1%.

[0040]

Example 2

A reaction was performed with the same method as in Example 1 except that the racemic 2-methylpiperazine in Example 1 was changed to an optically active (S)-2-methylpiperazine

(optically purity: 99.5% ee.) . As a result, the reaction yield of 1-benzyloxycarbonyl-3-methylpiperazine was 84.6% (based on the amount of 2-methylpiperazine), the optical purity was 99.5% ee., and a decrease of the optical purity did not occur.

[0041]

Example 3

A reaction was carried out as described for Example 1, except that the solvent in Example 1 was changed from 44 g of 1-butanol to a mixed solvent consisting of 4 g of water and 40 g of 1-butanol (water content 9.1 wt%). As a result, the reaction yield of 1-benzyloxycarbonyl-3-methylpiperazine was 72.9% (based on the amount of 2-methylpiperazine).

[0042]

Comparative Example 1

A reaction was carried out as described for Example 1, except that the solvent in Example 1 was changed from 44 g of 1-butanol to a mixed solvent consisting of 9 g of water and 35 g of 1-butanol (water content 20.5 wt%). As a result, the reaction yield of 1-benzyloxycarbonyl-3-methylpiperazine was 59.6% (based on the amount of 2-methylpiperazine).

[0043]

Comparative Example 2

A reaction was carried out as described for Example 1, except that the solvent in Example 1 was changed from 44 g of 1-butanol to a mixed solvent consisting of 22 g of water and

22 g of 1-butanol (water content 50 wt%). As a result, the reaction yield of 1-benzyloxycarbonyl-3-methylpiperazine was 33.6% (based on the amount of 2-methylpiperazine).

[0044]

Example 4

A reaction was performed with the same method as in Example 1 except that the solvent in Example 1 was changed from 44 g of 1-butanol to 44 g of ethanol (water content 0.06 wt%). As a result, the reaction yield of 1-benzyloxycarbonyl-3-methylpiperazine was 83.4% (based on the amount of 2-methylpiperazine).

[0045]

Comparative example 3

A reaction was carried out as described for Example 3, except that the solvent in Example 3 was changed from 44 g of ethanol to a mixed solvent consisting of 22 g of water and 22 g of ethanol. As a result, the reaction yield of 1-benzyloxycarbonyl-3-methylpiperazine was 37.7% (based on the amount of 2-methylpiperazine).

[0046]

Example 5

A reaction was performed with the same method as in Example 1 except that 5.0 g (= 0.0499 mol) of 2-methylpiperazine in Example 1 was changed to 12.5 g of (S)-2-methylpiperazine D-tartaric acid salt (as 2-methylpiperazine, 5.0 g = 0.0499 mol).

However, maturation is performed by stirring at 25°C for 12 hours. As a result, the reaction yield of 1-benzyloxycarbonyl-3-methylpiperazine was 85.9% (based on the amount of 2-methylpiperazine).

[0047]

Comparative Example 4

A reaction was carried out as described for Example 4, except that the solvent in Example 4 was changed from 44 g of 1-butanol to a mixed solvent consisting of 9 g of water and 35 g of 1-butanol (water content 20.5 wt%). As a result, the reaction yield of 1-benzyloxycarbonyl-3-methylpiperazine was 71.1% (based on the amount of 2-methylpiperazine).

[0048]

Comparative Example 5

A reaction was carried out as described for Example 4, except that the solvent in Example 4 was changed from 44 g of 1-butanol to a mixed solvent consisting of 18 g of water and 27 g of 1-butanol (water content 40.0 wt%). As a result, the reaction yield of 1-benzyloxycarbonyl-3-methylpiperazine was 51.6% (based on the amount of 2-methylpiperazine).

[0049]

[Effect of the Invention]

According to the present invention, an oxycarbonyl-substituted piperazine derivative can be produced with a high yield by oxycarbonylating a piperazine derivative

using a moderate condition and simple equipment.

[Name of Document]

[Abstract]

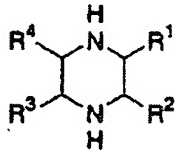
[Object]

To oxycarbonylate a piperazine derivative.

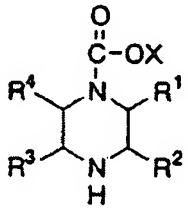
[Solving Means]

When an oxycarbonyl-substituted piperazine derivative represented with the general formula (2) is produced from a piperazine derivative represented with the general formula (1)

[Formula 1]



(1)



(2)

(where R^1, R^2, R^3 and R^4 represent an alkyl group, etc. having 1 to 4 carbon atoms, and X in the formula represents i) an alkyl group with 1 to 4 carbon atoms, ii) an alkenyl group with 1 to 4 carbon atoms, iii) an alkynyl group with 1 to 4 carbon atoms, iv) an aralkyl group not substituted in the aromatic ring, or substituted by an alkyl group with 1 to 4 carbon atoms or by an alkoxy group with 1 to 4 carbon atoms or by a halogen group, or v) an aryl group not substituted in the aromatic ring, or substituted by an alkyl group with 1 to 4 carbon atoms or by an alkoxy group with 1 to 4 carbon atoms or by a halogen group), an organic solvent having a water content of 15% or less is used.

[Selected Drawing] None